

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

TERBACIL

SB 950-166, Tolerance # 209

July 17, 1987

I. DATA GAP STATUS

Combined rat: Data gap, inadequate study, no adverse effect indicated.

Oncogenicity mouse: Data gap, inadequate study, possible adverse effect indicated.

Chronic dog: Data gap, inadequate study, no adverse effect indicated.

Repro rat: Data gap, inadequate study, no adverse effect indicated.

Terato rat: No data gap, no adverse effect.

Terato rabbit: No data gap, no adverse effect.

Gene mutation: No data gap, no adverse effect.

Chromosome: No data gap, no adverse effect.

DNA damage: No data gap, no adverse effect.

Neurotox: Not a required study at this time.

Note, Toxicology one-liners are attached

** indicates acceptable study

Bold face indicates possible adverse effect

II. TOXICOLOGY SUMMARY

COMBINED (CHRONIC TOXICITY AND ONCOGENICITY) STUDIES

Combined rat

015 36217 "Two Year Feeding Study in the Albino Rat" (IRDC, Report 125-010, 3/17/67) Sinbar Weed Killer (Terbacil, Herbicide 732) 80% WP formulation; several lots, purity nominal 80%; 0, 50, 250 or 2500 (graduated over time to 10,000) ppm in the diet, to 36 rats/sex/group; Liver toxicity at the high doses (2500 or 10000 ppm) centrilobular cell enlargement and vacuolation. No adverse effect indicated. Apparent NOEL = 250 ppm (hepatotoxicity). **Not acceptable for onco or chronic toxicity requirement,**

incomplete, not upgradable. (Routine histopathology limited to animals surviving to scheduled sacrifice, supplemented by microscopic inspection of

selected gross lesions; inconsistent dosing, inadequate characterization of test article, intercurrent disease.) (RAM) C. Aldous, 10/29/85.

010 14816 Prior review of 015 36217. Summary only. Data incomplete for assessment. Concern expressed over administration of antibiotics, tetracycline and penicillin which may have produced toxic symptoms alone, or upon interaction with the test substance. Absorption may have been influenced by antibiotic effect on gut flora. (NLH) JP Christopher, 5/14/85.

022 50601 Supplement to 015 36217. Dosing analysis. Doses ranged from 50% of target to 280%, with over half of the sample data (Table II) outside range of +/- 20% of target. (RAM) CN Aldous 7/17/87 (considered in rebuttal response).

Chronic dog

016 36214 "Two Year Feeding Study in the Dog" (IRDC Report #125-011, 3/17/67) Sinbar Weed Killer 80% WP (nominal 80% terbacil), no purity data, several lots; 0, 50, 250 or 2500 ppm (high dose increased to 10000 ppm during the 26th to 46th week) in the diet of 4 beagle dogs/sex/group. Liver enlargement occurred at the high dose but toxicity was not characterized in histopathology or blood chemistry. Apparent NOEL = 250 ppm. **Unacceptable, possibly upgradable.** (No evidence of achieving the MTD, toxicity not characterized.) (DAS) CN Aldous 11/22/85.

010 14815 Summary of report 016 36214. No data presented. (NLH) JP Christopher 5/14/85.

Oncogenicity, mouse:

3.

010 14817 "Two-Year Feeding Study in Mice" (IRDC, Report No. 125-027, 6/19/81); terbacil technical, lot H-11086; purity = 97.8%; 0, 50, 1250, or 5000 (increased to 7500 at week 54) ppm in the diet of 80 CD-1 mice/sex/group. Statistically significant dose related increase in mortality in males, very likely coincidental, and **not** indicative of a significant adverse human health effect because the dose was quite high. General systemic effects NOEL = 50 ppm (liver effects in males: dose-related centrilobular hepatocyte hypertrophy at 1250 ppm upward, [non-neoplastic] hyperplastic nodules at 5000/7500 ppm). **Possible adverse effects:** Increased incidence of lung adenomas in all treated groups compared to concurrent controls. **Incomplete, but upgradeable.** (NLH) JP Christopher 5/13/85 [which review concluded study **not acceptable**, based on "insufficient information for evaluation"]. Subsequent review considered original submission and data indicated below and found issues of previous review successfully addressed, however there are questions associated with materials received since the first review: (RAM)/ C. Aldous, 7/14/87. File = 166MOO1.CNA

022 50600 Supplement to study 010:14817. Dosing analysis. Eight sample dates; all within 80% to 106% of target. (RAM) C. Aldous 7/14/87.

024, 025 50605, 50606 (Supplement to 010 14817) individual data, complete report (June 19, 1981 original report). (RAM) C. Aldous 7/14/87.

013 36212 Exact duplicate of 025:050606.

014 36213 (Amendment dated 1/31/83) Re-evaluation of lung tumor incidence, revised statistics (no change in relative frequency. Possible treatment effect.) (RAM) C. Aldous 7/14/87

026 050607 Imperfect duplicate of 014:36213.

TERATOLOGY STUDIES

Rat Teratology

026 50608 "Teratogenicity Study in Rats with 3-tert-butyl-5-chloro-6-methyluracil (IND 732)" (Haskell Laboratories, report # 481-79; 2/20/80) Terbacil 96.6%; lot T-81115-D; 0, 250, 1250 or 5000 ppm administered in the diet to 19 to 22 pregnant rats/group. Maternal NOEL = 250 ppm (apparently treatment-related decrement in body weight gain in higher dose dams during first 5 days of treatment. Same groups had lower feed consumption, hence weight gain differences could be due to either toxicity or feed rejection). No other maternal toxicity observed. No dose related developmental effects observed. Developmental NOEL > 5000 ppm (391.9 mg/kg/day). **Acceptable. (RAM) CN Aldous 7/16/87. File = 166RTT1.CNA

EPA One-liner: No teratogenicity. Embryotoxicity NOEL = 250 (decrease of number of implantations and live fetuses). Maternal NOEL = 250 ppm (reduction in body weight).

022 50602 Supplement to 026 50608. Exact duplicate of 026:050609. Dose analysis. Samples ranged from 98% to 120% of target dose under 4 storage regimes. Acceptable in support of primary study. (RAM) CN Aldous 7/16/87.

022 50999 Supplement to 026 50608. Registrant rebuttal to EPA comments. Test group consisted of two breeding lots which, when analyzed separately, show significant differences in number of implantations between breeding lots: specifically, between the two high dose lots and between the two control lots. Incidence of hydroureter and hydronephrosis not significant for any or all test groups compared to historical controls with Fisher's exact test. Such alterations have been associated with developmental delay. (RAM) CN Aldous 7/16/87.

018 36216 Summary of 026 50608. Possible adverse effect indicated by reviewer, based on information in this incomplete report (apparent treatment-related decrease in implantations and live fetuses/litter). **Unacceptable, incomplete.** (Every other page missing). (DAS) CN Aldous 11/22/85.

010 14813 Summary of 026 50608. Dose in feed considered inappropriate by reviewer, gavage preferred. No data presented. (NLH) JP Christopher 5/10/85.

Rabbit teratology

026 50610 "Embryo-fetal toxicity and teratogenicity study of Terbacil by gavage in the rabbit". Haskell Labs, 2/21/84. Terbacil, 96.1%. 0, 30, 200, or 600 mg/kg/day by gavage in 0.5% methyl cellulose suspension. Maternal NOEL = 200 mg/kg/day (excess deaths or in extremis sacrifices. Many dams, particularly in high dose group, had hairballs in stomach, which were associated with anorexia and associated weakness and death. Even high dose dams **without hairballs lost weight or had reduced weight gain, and one of 5 pregnant high dose dams suffered total litter loss. Developmental effects NOEL = 200 mg/kg/day (reduced fetal body weight, possibly treatment related fused ribs and sternebrae, delayed ossifications). No adverse health effect indicated. **Acceptable.** RAM/ C. Aldous, 7/17/87. File (for portion of review only) = 166RBT1.CNA

010 14813 Summary of 026:50610, above. Unacceptable (summary report only). J. Christopher, 5/14/85.

REPRODUCTION STUDIES

Rat Reproduction

017 36215 "Three Generation Reproduction Study in the Rat" (IRDC Report #125-012, 3/23/67) Sinbar Weed Killer 80% WP (nominal 80% terbacil), no purity data, several lots; 0, 50 or 250 ppm in the diet of 10 male and 20 female rats/group. No toxicity or reproductive effects reported. NOEL > 250 ppm. **Unacceptable and not upgradable.** (Inadequate dose) (DAS) CN Aldous 11/22/85.

010 14813 Brief summary of report 017 36215, no individual data. (NLH) JP Christopher 5/14/85.

010 14814 Summary of reproduction study 017/026:36215.

022 50601 Supplement to 017 36215 (same analysis as for 015 36217, concurrent chronic rat study; referenced per rebuttal volume 022 item #17) Dosing analysis. Doses ranged from 50% of target to 280%, with over half of the sample data (Table II) varying from target by more than 20%. (RAM) CN Aldous (see Rebuttal Response document of 7/17/87).

MUTAGENICITY STUDIES

Gene mutation

010 14820 "CHO/HGPRT Assay for Gene Mutation with Terbacil"; (Haskell Laboratory Report No. 87-84; 1/31/84); Terbacil 96.1% (lot no. T00126); 0, 0.5, 2.0, 3.0, 4.0, 5.0 or 6.0 mM concentrations with or without rat liver S-9 activation; 2 trials, 5 plates/trial. Cytotoxic at 2.75 mM with activation or 3.0 mM without activation. No significant increase in mutation frequency observed. No adverse effect indicated. **Acceptable. (NLH) JP Christopher 5/13/85.

Chromosome aberration

**026 050612 (complete report for 14818) "In vivo Assay for Chromosome Aberrations in Rat Bone Marrow Cells." (Hazleton Biotechnologies, 10/26/84, Study 201-723) Terbacil, 96.1%, lot T00126; given by oral gavage to 15/sex/group at 0, 20, 100 or 500 mg/kg, single dose, with sacrifices of 5/sex/group at 6, 24 or 48 hours; cyclophosphamide as positive control with 5/sex sacrificed at 24 hours; Sprague-Dawley CD albino rats; scored 50 metaphases per animal where possible; no deaths but clinical signs of depression, labored respiration and soft feces at 500 mg/kg - also weight loss from treatment time to 24 hours with some gain by 48 hour sacrifice in high dose group, especially; no increase in chromosomal aberrations or change in mean number of chromosomes reported; initially evaluated as unacceptable due to missing pages in the report. These have been supplied as Record # 050612. Study is upgraded to acceptable status with no adverse effect reported. JPC, 5/13/85 and JG, 7/16/87 File = 1B: 166843A.JG

010 14818 Incomplete version of 026 50612; alternate pages missing.
Unacceptable, incomplete.(NLH) JP Christopher 5/13/85.

DNA damage

010 14821 "Unscheduled DNA Synthesis/Rat Hepatocytes In Vitro" (Haskell Laboratory Report No. 379-84, 8/21/84) Terbacil 96.1%, Lot No. T00126; 0, 0.01, 0.033, 0.10, 0.33, 1.0, 2.5, 5.0, 7.5 or 10.0 mM duplicate plates, repeat trial. Cytotoxic at 5.0 mM. No evidence of unscheduled DNA synthesis.Acceptable.**(NLH) JP Christopher 5/13/87.

NEUROTOXICITY STUDIES

Neurotoxicity

Not a required study at this time.